REMARKS

Claims 1-3, 6, 7, 10-12, 15-21, and 41 are pending in the application and under active consideration.

35 U.S.C. § 103

Claims 1-3, 6, 7, 10-12, 15-19, and 41 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Gorczynski et al. (Cellular Immunol. (1995) 160:224-231; hereinafter "Gorczynski") in view of Nakai et al. (Blood (1998) 91:4600-4607; hereinafter "Nakai"), and further in view of Wakita et al. (J. Biol. Chem. (1998) 273:9001-9006; hereinafter "Wakita"). Wakita is cited for teaching that conditional transgene expression of HCV transgenes in the liver of a trangenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. Gorczynski is cited for teaching the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of an animal. Nakai is cited for teaching a method for sustained expression of a transgene in the liver of an animal for more than a month.

In maintaining the rejection, the Office Action alleges that it would have been obvious to one of ordinary skill in the art to create an animal model for screening agents that modulate tolerance to an HCV immunogen in view of the teachings of the combination of cited references:

> Specifically, the prior art teaches: (1) the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal (Gorczynski), (2) that a protein of interest can be expressed in the liver of an animal for more than a month using an adeno-associated viral particle encoding the protein of interest when the viral particle is delivered by portal vein delivery (Nakai; e.g., see Table 1, Figure 5, etc.), and (3) a mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection (Wakita). (Office Action, page 8.)

The Office Action asserts that one of ordinary skill in the art would have been motivated to combine these references because:

> In this case, the teachings of Wakita that an animal that expresses an HCV transgene in its liver is an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" provides the motivation for combining the references. Furthermore, one of ordinary skill in the art would have the knowledge to

> recognize that portal injection of a vector that expresses a protein is a convenient way of producing an animal that expresses a foreign gene, thus providing further suggestion and motivation to combine the references. (Office Action, page 13.)

The Office Action further asserts that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references" (Office Action, page 8).

In addition, claims 1-3, 6, 7, 10-12, 15-21, and 41 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Gorczynski et al. (*supra*) in view of Nakai et al. (*supra*), and further in view of Wakita et al. (*supra*) and further in view of Donnelly et al. (WO 97/47358; hereinafter Donnelly). Donnelly is cited for teaching that the HCV NS5a gene could be use used to raise an immunological response to HCV in an animal. The Office Action alleges that one or ordinary skill in the art would have been motivated to make an HCV NS5a tolerant animal "in view of the teaching of Donnelly that HCV NS5a is a specific immunogenic gene" (Office Action, page 6).

Applicants respectfully traverse the rejections under 35 U.S.C. § 103 and the Office's purported facts underlying the rejections on the following grounds.

A. Applicants Have Properly Addressed the References In Combination

The assertion that Applicants have addressed the references individually is without merit. In fact, Applicants' previous arguments properly summarized the relevant case law, addressed the teachings of each reference, addressed the lack of motivation within the references to combine them as suggested by the Office and, in addition, addressed the lack of the reasonable expectation that such a combination would be successful.

To reiterate, there are no suggestions in Gorczynski, Nakai, Wakita and Donnelly to arrive at the claimed methods. The pending claims are directed to methods for preparing a non-human animal for screening for agents that modulate tolerance to an HCV immunogen. Previously described transgenic animal models do not provide good models of tolerance because transgenic animals, which express HCV antigens at birth, are inherently tolerant to those antigens. The immune system views antigens present at birth as "self" antigens; therefore, animal models in which the antigens are expressed at birth, do not provide a model of tolerance

to non-self antigens. In contrast, the instant application provides a non-germline animal model of tolerance that more accurately mimics the natural development of tolerance during chronic HCV infection. See the specification, for example, at page 3, lines 10-29.

The focus of Gorczynski is on methods of delaying transplant rejection of skin allografts by injection of lymphoid or spleen cells into the portal vein of an animal. Gorczynski fails to describe anything pertaining to HCV. In particular, Gorczynski fails to describe expression of antigens in the liver, let alone a nucleic acid encoding an HCV immunogen. Nor does Gorczynski describe or suggest delivering a nucleic acid encoding an immunogen to the liver of an animal by injection through the portal vein. Furthermore, Gorczynski fails to describe or suggest any method for achieving sustained expression of an HCV immunogen in the liver for at least one month in order to induce immunological tolerance. Thus, Gorczynski fails to disclose or suggest any method for preparing an animal for screening for agents that modulate tolerance to HCV.

Moreover, Gorczynski fails to describe an animal in which the presence of any non-self antigens is sustained for at least one month. On the contrary, Gorczynski describes the injection of lymphoid or spleen cells into the portal veins of mice a few days before graft transplants to delay transplant rejection. In one study by Gorczynski et al., mice received skin grafts 36 hours after injection of cells in the portal vein and were sacrificed within 120 hours of receiving skin grafts (see page 226, col. 2). In a second study, mice were monitored until their skin grafts were rejected. All mice rejected their skin grafts within 22 days (see FIG. 2 at page 227). In no case, was long term tolerance to grafts achieved. Thus, Gorczynski fails to describe or suggest any animal model in which the presence of antigen is sustained for more than one month to achieve tolerance.

The secondary reference of Nakai also fails to even mention HCV, let alone, teach or suggest any method of preparing an animal model of tolerance to HCV antigens. With regard to the Examiner's assertions that Nakai teaches sustained expression of a gene in the liver (see Office Action, page 3), Applicants respectfully point out that Nakai fails to describe or suggest expression of any HCV antigens. Nor does Nakai disclose anything about immunological tolerance. Rather, Nakai describes transduction of murine hepatocytes with recombinant adeno-associated virus vectors expressing human factor IX for the purpose of developing methods of

gene therapy for hemophilia B. Factor IX is an endogenous protein normally synthesized in the liver (see, *e.g.*, page 4600, first column). Thus, **human Factor IX is not an immunogen** as claimed in the present application and would not be expected to produce an immune response. Nakai fails to teach or suggest any method for inducing tolerance to antigens in an animal model, as claimed.

Wakita pertains to Cre/loxP-mediated conditional expression of HCV proteins in transgenic mice. Wakita is silent on immunological tolerance to HCV antigens. Wakita fails to describe or suggest sustained expression of HCV antigens for at least one month in order to achieve immunological tolerance, as claimed. Rather, Wakita can be described as teaching away from the claimed invention, in that the Cre/loxP system is used to control expression of HCV transgenes such than antigens are produced only transiently in order to generate an antibody response (see page 9006, col. 1). Generation of antibody responses is the contrary of generation of tolerance. As defined in the instant application, ""tolerance" or "tolerant" refers to an immunological state in which the effector cells of the immune system do not respond to an immunogen and do not become activated upon contact with the immunogen" (see page 5, lines 21-23, underlines were added for emphasis), which means antibodies are not generated against the immunogen. Furthermore, the transgenes encoding HCV antigens are injected into fertilized mouse eggs to produce transgenic animals as described in Wakita, rather than injected in the portal vein of an animal, as claimed in the instant application.

There is nothing in the secondary reference of Donnelly to cure the deficiencies of Gorczynski, Nakai, and Wakita. Donnelly has nothing to do with immunological tolerance to HCV. On the contrary, the focus of Donnelly is on therapeutic and prophylactic vaccines capable of eliciting an immune response against HCV. Donnelly describes intramuscular injection of polynucleotides encoding HCV antigens to generate antibody and CTL immune responses against HCV. See, *e.g.*, page 5, lines 25-27 and page 11, lines 29-33. Donnelly fails to teach or suggest anything regarding nucleic acid immunization by injection in the portal vein, or sustained expression of antigens in the liver to achieve immunological tolerance. Thus, the cited combination fails to disclose or suggest the methods as claimed.

It is impermissible to apply an "obvious to try" standard for a rejection under 35 U.S.C. § 103. As set forth by *In re Goodwin, Margrave, and Wagner*, 198 USPQ 1 (CCPA 1978):

> [T]his court has consistently refused to recognize "obvious to try" rejections. "As we have said many times, obvious to try is not the standard of 35 USC 103. In re Tomlinson, 53 CCPA 1421, 363 F.2d 928, 150 USPQ 623 (1966). Disregard for the unobviousness of the results of 'obvious to try' experiments disregards the 'invention as a whole' concept of §103 * * *." In re Antonie, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977) (emphasis in original).

The references do not, alone or in any combination, teach or suggest the claimed methods of preparing a non-human animal for screening for agents that modulate tolerance to an HCV immunogen, as claimed. Gorczynski's methods use cells, not nucleic acids encoding antigens, do not sustain the presence of antigen for at least one month as required by the claims, and fail to achieve long-term immunological tolerance. Nakai focuses on gene therapy for hemophilia by expression of Factor IX in the liver. Nakai fails to describe or suggest expression of any other gene in the liver, let alone sustained expression of antigens for inducing tolerance. Therefore, in contrast to the instant application, neither Gorczynski nor Nakai teach or suggest sustaining expression of nucleic acids encoding HCV antigens in the liver to achieve tolerance to HCV infection. Wakita also fails to teach or suggest any method for achieving tolerance to HCV antigens. On the contrary, Wakita focuses on antibody responses after transgene activation. Finally, Donnelly also has nothing to do with immunological tolerance, but rather, pertains to vaccines that generate an immune response, which is the contrary of tolerance.

B. No Motivation to Combine the Teachings of the Cited References

In the instant case, there is no motivation to combine the individual elements of the references in the manner set forth by the Examiner. The Examiner cited MPEP 2143.01 to assert that the motivation existed because the combined teachings, the knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art that the cited references could be combined to make the claimed invention in the instant case with a reasonable expectation of success. Applicants respectfully disagree for at least the reasons set forth below.

In referring to the transgenic mouse taught by Wakita as a "powerful tool with which to investigate the immune responses and pathogenesis of HCV infection," which supposedly provides the motivation to combine the references (Office Action, pages 6 and 13), the Examiner

appears to have misapplied or misunderstood the applicability of the teachings of Wakita. Immune responses are not the same as tolerance. Pathogenesis is not the same as tolerance, either. As defined in the instant application, ""tolerance" or "tolerant" refers to an immunological state in which the effector cells of the immune system do not respond to an immunogen and do not become activated upon contact with the immunogen" (see page 5, lines 21-23, underlines were added for emphasis), which is the contrary of the immune responses as described in Wakita. In addition, the use of a transgenic mouse, expressing HCV structural proteins, by Wakita does not automatically suggest an animal model of tolerance, let alone for screening agents that modulate tolerance, as described in the instant application. Wakita fails to even mention immunological tolerance, nor using the transgenic mouse as a model of tolerance. Nor does Wakita suggest any non-germline animal model. As mentioned above, transgenic animals are less desirable as models of tolerance because of the presence of antigens at birth. Thus, the motivation to combine the references cannot derive from Wakita.

The only other reference cited that has anything to do with HCV is Donnelly, but Donnelly teaches vaccines for inducing an immune response to HCV, again the contrary of tolerance. Therefore Donnelly cannot provide the motivation to combine the references.

Nakai fails to teach anything about expression of HCV immunogens in the liver or immunological tolerance. The fact that Factor IX expression can be sustained in the liver for treatment of hemophilia is irrelevant to the current invention.

Gorczynski is cited as supposedly teaching "the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal" (Office Action, page 14). However, Gorczynski fails to describe sustaining the presence of an antigen in the liver for at least one month or preferably the life of an animal in order to achieve tolerance, as described in the instant application (see specification, *e.g.*, at page 7, lines 8-11). All of the mice tested by Gorczynski rejected their skin grafts within one month. Furthermore, the mice failed to remain unresponsive to their skin grafts in spite of their pretreatment with cells before the transplant and their continued exposure to skin graft antigens after the transplant. Thus, Gorczynski fails to describe successfully sustaining tolerance in an animal model.

Furthermore, none of the references even mention an animal model of HCV immunological tolerance, nor screening such a model for agents that modulate tolerance. Absent experimental evidence in the references themselves that sustained expression of an HCV immunogen in the liver for at least one month would work in achieving tolerance, a *prima facie* case of obviousness cannot be made. Simply put, the references do not provide the requisite motivation to combine their teachings as set forth in the Office Action.

Regarding the knowledge of one of ordinary skill in the art which was cited by the Examiner as part of the motivation to combine the references, Applicants respectfully point to MPEP 2144.03 as part of response. MPEP 2144.03 indicates:

> "Reliance on Common Knowledge in the Art or "Well Known" Prior Art [R-1]
>
> A. ...
>
> It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. Zurko, 258 F.3d at 1385, 59 USPQ2d at 1697 ("... The board cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies.")."

Applicants respectfully submit that the Examiner did not provide evidentiary support in the record for this "knowledge of one of ordinary skill in the art" or the rationale on which he relied on arriving the conclusion.

C. No Reasonable Expectation of Success

One would not have the reasonable expectation of success in producing an animal model for screening for agents that modulate tolerance to HCV immunogens based on the methods described in the cited references. Gorczynski has the distinction of being the only reference that even mentions immunological tolerance. However, Applicants reiterate that Gorczynski fails to describe sustaining the presence of antigen in the liver or successfully maintaining tolerance in an animal model.

Although Nakai teaches the sustained expression of Factor IX in the liver, the presumption that methods of expressing Factor IX are necessarily applicable to other genes is unsupported. Nakai fails to demonstrate that expression of HCV immunogens can be sustained.

Therefore, any suggestion that genes other than Factor IX would be successfully expressed in the liver by the methods described is unsupported by any experimental evidence.

Notably absent from the other references is any teaching whatsoever regarding immunological tolerance or any methods of producing an animal model for testing agents that modulate tolerance, as claimed.

D. Conclusion

Virtually all inventions are combinations of elements that can be individually identified in multiple references. However, the mere identification in a reference of individual components of claimed limitations cannot be a basis for an obviousness rejection. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in references. *See, e.g., In re Kotzab,* 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). The main reference cited by the Examiner for providing this motivation, Wakita, taught an animal model that is different from what the instant application taught and claimed it to be a powerful tool to investigate immune responses that are the contrary of the tolerance state as taught and claimed in the instant application. Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicant invites the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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